# Transcranial Magnetic Stimulation*

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## DESCRIPTION

### Transcranial Magnetic Stimulation (TMS)

Transcranial Magnetic Stimulation (TMS) is a noninvasive method of delivering electrical stimulation to the brain. A magnetic field is delivered through the skull, where it induces electric currents that affect neuronal function. A variety of TMS modalities have been developed, which differ on parameters including stimulation intensity, frequency, pattern, and site of the brain stimulation.

TMS is also being studied as a treatment for a variety of other disorders including but not limited to chronic pain, obsessive-compulsive disorder (OCD), post-partum depression, depression associated with Parkinson's disease, schizophrenia, migraine, tinnitus, autism, eating disorders, fibromyalgia and other miscellaneous conditions.

In contrast to electroconvulsive therapy, transcranial magnetic stimulation can be performed in an office setting as it does not require anesthesia and does not induce a convulsion.

**Defining Major Depression**
A major depressive episode as defined in the DSM-5 implies a prominent and relatively persistent (e.g., nearly every day for at least two weeks) depressed or dysphoric mood that represents a change from previous functioning, and includes at least five of the following nine symptoms, one of which is either of the first two symptoms.

- Depressed mood
- Markedly diminished interest or pleasure in usual activities
- Significant change in weight and/or appetite
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Feelings of worthlessness or excessive or inappropriate guilt
- Slowed thinking or impaired concentration
- Recurrent thoughts of death or suicidal ideation or a suicide attempt

Response is clinically defined as an improvement in symptoms from the initial onset of depression. The term remission has typically been applied to being symptom free or having minimal symptoms, representing an end to the immediate episode.

- The DSM-5 defines remission as a period of two or more months with no symptoms or only 1-2 mild symptoms.
- Partial remission involves significant improvement, but mild symptoms of major depressive disorder (MDD) are still present or there are no longer any significant symptoms of a Major Depressive Episode, but the period of remission has been less than two months.
- Recovery is the absence of symptoms for at least four months following the onset of remission with periods of improvement.
- Relapse has been defined as the re-emergence or early return of the depressive episode of full or significant depressive symptoms after remission.

**Transcranial Magnetic Stimulation (TMS) Types**

| Type | Definition |
|---|---|
| **Accelerated** | Proposes an accelerated treatment schedule, using multiple sessions per day for fewer weeks duration. |
| **Bilateral** | Combines high frequency stimulation of the left dorsolateral prefrontal cortex (DLPC) with low frequency stimulation of the right DLPC (either simultaneously or sequentially) each session. |

| | |
|---|---|
| **Conventional (Repetitive)** | High frequency stimulation is delivered over the left dorsolateral prefrontal cortex (DLPFC) or low frequency stimulation over the right DLPFC.<br><br>A treatment course of conventional TMS should not exceed 5 days a week for 6 weeks (total of 30 sessions), followed by a 3-week taper of 3 TMS treatments in week 1, 2 TMS treatments the next week, and 1 TMS treatment in the last week. |
| **Deep** | Deep TMS employs an H-coil helmet designed to encompass a broader surface area and stimulate deeper brain structures than conventional TMS. |
| **High dose** | Delivers more pulses than usual over the same treatment time frame (e.g., 6000 pulses per session instead of 3000). |
| **Maintenance Therapy** | Maintenance therapy can be considered as:<br>• Prolonged treatment sessions of initial or repeat courses of therapy which may or may not be at a lower dose, to maintain improvement/results.<br>• Repeating or continuing therapy within the same episode: meaning no remission has occurred or additional sessions prior to documented relapse. |
| **Theta Burst /Intermittent Theta-Burst Stimulation (iTBS)/Express TMS** | Theta burst stimulation is administered at lower intensities and shorter intervals than conventional TMS.<br><br>(2022 UptoDate) According to Holtzheimer et al. "Theta burst TMS — Theta burst repetitive TMS involves magnetic pulses that are administered at 50 hertz five times per second and are intended to mimic endogenous theta rhythms; this approach appears to exert longer lasting effects upon motor cortex excitability than conventional repetitive TMS and requires less stimulation time (e.g., 6 minutes per session rather than 30 to 40 minutes)."<br><br>Theta burst stimulation may be administered using an accelerated protocol. One example of an accelerated theta burst protocol is the Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) protocol, consisting of 10 daily sessions over 5 consecutive days. |

**Monitoring Treatment Efficacy**

Evidence currently supports the use of transcranial magnetic stimulation (TMS) for moderate and severe major depressive episode with no psychotic symptoms that is treatment-resistant or treatment-intolerant. The following self-report rating scales and their respective scorings could guide toward moderate and severe major depressive symptomatology:

- A score of at least 24 on the Beck Depression Inventory indicates mid-range of moderate depression symptomatology and would therefore be appropriate for transcranial magnetic stimulation treatment.
- Based on clinical studies and moderate depression symptomatology, a score of at least 4 on the Clinical Global Impressions Severity of Illness (CGI-S) would therefore be appropriate for transcranial magnetic stimulation treatment.
- Based on clinical studies and moderate depression symptomatology, a score of at least 20 on the Hamilton Rating Scale for Depression 17-item (HAM-D) would therefore be appropriate for transcranial magnetic stimulation treatment.
- A score of at least 32 on the Inventory for Depressive Symptomatology Self-Report (IDS-SR) indicates mid-range of moderate depression symptomatology and would therefore be appropriate for transcranial magnetic stimulation treatment.
- Based on clinical studies and moderate depression symptomatology, a score of at least 20 on the Montgomery Asberg Depression Rating Scale (MADRS) would therefore be appropriate for transcranial magnetic stimulation treatment.
- A score of at least 13 on the Patient Health Questionnaire (PHQ-9) indicates mid-range of moderate depression symptomatology and would therefore be appropriate for transcranial magnetic stimulation treatment.
- A score of at least 13 on the Quick Inventory of Depressive Symptomatology (QIDS) indicates mid-range of moderate depression symptomatology and would therefore be appropriate for transcranial magnetic stimulation treatment.

Additional research is needed to determine the durability of remission produced by TMS.

**Treatment-Resistant Depression (TRD)**

**Clinical Context and Therapy Purpose**
The purpose of transcranial magnetic stimulation (TMS) is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with TRD.

**Patients**
The relevant population of interest are individuals with TRD.

Patients with TRD are actively managed by psychiatrists and other mental health professionals in an outpatient clinical setting.

**Interventions**
The therapy being considered is TMS.

**Comparators**
The following therapies are currently being used to treat TRD: pharmacotherapy, psychological therapy, behavioral therapy, and electroconvulsive therapy (ECT).

**Outcomes**
The general outcomes of interest are reductions in symptoms and improvements in quality of life and functional outcomes. Follow-up over months is of interest to monitor outcomes.

(2019) According to Rizvi et al. **t**he clinical efficacy of TMS as an antidepressant has been well established. TMS is an innovative and promising treatment modality for patients with treatment resistant depression (TRD). Patient compliance, however, may be affected, as TMS requires frequent visits to the clinic. Neuromodulation through TMS may induce neurogenesis. Further research is required to explore its therapeutic implementation and limitations, providing more effective treatment of patients with TRD.

(2015) Levkovitz et al. concluded *Major depressive disorder* (MDD) is a prevalent and disabling condition, and many patients do not respond to available treatments. Deep transcranial magnetic stimulation (dTMS) is a new technology allowing non-surgical stimulation of relatively deep brain areas. This is the first double-blind randomized controlled multicenter study evaluating the efficacy and safety of dTMS in MDD. We recruited 212 MDD outpatients, aged 22-68 years, who had either failed one to four antidepressant trials or not tolerated at least two antidepressant treatments during the current episode. They were randomly assigned to monotherapy with active or sham dTMS. Twenty sessions of dTMS (18 Hz over the prefrontal cortex) were applied for 4 weeks acutely, and then biweekly for 12 weeks. Primary and secondary efficacy endpoints were the change in the Hamilton Depression Rating Scale (HDRS-21) score and response/remission rates at week 5, respectively. dTMS induced a 6.39-point improvement in HDRS-21 scores, while a 3.28-point improvement was observed in the sham group (p=0.008), resulting in a 0.76 effect size. Response and remission rates were higher in the dTMS than in the sham group (response: 38.4 vs. 21.4%, p=0.013; remission: 32.6 vs. 14.6%, p=0.005). These differences between active and sham treatment were stable during the 12-week maintenance phase. dTMS was associated with few and minor side effects apart from one seizure in a patient where a protocol violation occurred.

The results suggest that dTMS constitutes a novel intervention in MDD, which is efficacious and safe in patients not responding to antidepressant medications, and whose effect remains stable over 3 months of maintenance treatment.

**Accelerated Transcranial Magnetic Stimulation in the Treatment of Major Depressive Disorder**
(2016) Phillip et al. completed a 12-month multisite randomized pilot study. They noted repetitive transcranial magnetic stimulation (TMS) is now widely available for the clinical treatment of depression, but the associated financial and time burdens are problematic for patients. Accelerated TMS (aTMS) protocols address these burdens and attempt to increase the efficiency of standard TMS. This systematic review and meta-analysis aimed to examine accelerated TMS studies for depressive disorders in accordance with PRISMA guidelines. Inclusion criteria consisted of studies with full text

publications available in English describing more than one session of TMS (repetitive or theta burst stimulation) per day. Studies describing accelerated TMS protocols for conditions other than depression or alternative neuromodulation methods, preclinical studies, and neurophysiology studies regarding transcranial stimulation were excluded. Eighteen articles describing eleven distinct studies (seven publications described overlapping samples) met eligibility criteria. A Hedges' g effect size and confidence intervals were calculated. The summary analysis of three suitable randomized control trials revealed a cumulative effect size of 0.39 (95% CI 0.005-0.779). A separate analysis including open-label trials and active arms of suitable RCTs revealed a g of 1.27 (95% CI 0.902-1.637). Overall, the meta-analysis suggested that aTMS improves depressive symptom severity. In general, study methodologies were acceptable, but future efforts could enhance sham techniques and blinding.

**Miscellaneous Conditions for Transcranial Magnetic Stimulation (TMS) Therapy**

**Bipolar Disorder (BD)**

(2021) McGirr et al. completed a randomized clinical trial on the efficacy if active vs. sham intermittent theta burst transcranial magnetic stimulation for patients with bipolar depression and concluded iTBS targeting the LDLPFC does not appear to be clinically efficacious in the treatment of bipolar depression in conjunction with an antimanic agent. Although iTBS does not appear to be associated with increases in manic symptoms in general, we cannot eliminate the possibility that it may result in increased risk of treatment-emergent affective switches. This negative RCT highlights the importance of standardizing protocols and testing the efficacy of neurostimulation treatments proven in MDD in BD. Furthermore, standardizing protocols and sham-controlled designs to account for spontaneous response is necessary to determine what, if any, role TMS has in the treatment of bipolar depression.

(2020) Goldwaser et al. completed a retrospective analysis of bipolar depression treated with transcranial magnetic stimulation. A total of 44 patients with BD were identified, representing 15% of the total TMS population. 77% of those who completed a course of TMS met response criteria, and 41% of subjects who completed at least 25 treatments met remission criteria. Subjects with BD1 were more likely to respond, remit, or suffer an adverse event than those with BD2. No patient met clinical criteria for a manic/mixed episode, but four (10%) discontinued due to concerns of activation. Limitations of this study exist inherent to methodologic concerns in retrospective chart data gathering. For one, we are unable to more fully discern qualitative aspects of TMS effects outside of the few parameters captured by the MADRS. Quality of life measures have been shown to be improved in neuromodulation-responsive populations of affective disorder patients, even when null improvements are reported with standardized depression rating scales (Conway et al., 2018), suggesting there may be an underestimation of the actual benefits TMS may have. Moreover, confounds such as differential psychopharmacology and medical comorbidities were not accounted for as covariates in biostatistical considerations, as was not the aim of this report, but would certainly be needed for future, larger-scale validation studies addressing this question. The authors concluded results reported here suggest that

TMS for bipolar depression is both more successful and more prone to adverse events than a similar unipolar population. To this end, a higher percentage of bipolar patients responded to TMS and required fewer treatments to see an effect than for unipolar patients in our experience. This higher risk–benefit ratio is greater for BD1 than BD2 patients.

While these results support the continued development of TMS for bipolar depression, care must be taken to make sure patients are adequately mood stabilized and fully in the depressive phase of the illness before commencing treatment, despite the low probability of affective switching. Much is left to be deciphered in this exciting area of neuromodulation, and a larger, open-label prospective study would be more able to address some of the yet unanswered and vital questions remaining prior to pursuing mainstay administration of TMS to bipolar depressed patients.

(2020) Tee et al. conducted a systematic review and meta-analysis of sham controlled RCTs of rTMS for the treatment of bipolar disorder. Eight trials of rTMS in bipolar depression showed small but statistically significant improvements in depression scores compared to sham control (standardized mean difference = 0.302, $P < 0.05$). rTMS appears safe and effective in treating bipolar depression. However, most studies had a high risk of bias which could have exaggerated the treatment effects. The effect of rTMS was inconclusive in bipolar mania due to the high heterogeneity and limited number of controlled trials. The authors concluded rTMS is an effective treatment option for bipolar depression. However, most studies had inadequate randomization and could lead to exaggerated estimates of treatment effects. The effect of rTMS over right prefrontal cortex is inconclusive in the treatment of mania. More stringent RCTs in this area will still be needed before the treatment can be recommended in BD.

**Chronic Pain**

(2018) Cochrane review by O'Connell et al identified 42 RCTs (range 4 to 70 participants) on TMS for chronic pain. Meta-analysis of rTMS studies vs sham for pain intensity at short-term follow-up (0 to < 1-week postintervention), (27 studies, involving 655 participants), demonstrated a small effect with heterogeneity (SMD -0.22, 95%CI -0.29 to -0.16, low-quality evidence). This equates to a 7% (95% CI 5% to 9%) reduction in pain, or a 0.40 (95% CI 0.53 to 0.32) point reduction on a 0 to 10 pain intensity scale, which did not meet the minimum clinically important difference threshold of 15% or greater. There is very low-quality evidence that single doses of high frequency rTMS of the motor cortex and Transcranial direct current stimulation (tDCS) may have short-term effects on chronic pain and quality of life, but multiple sources of bias exist that may have influenced the observed effects. We did not find evidence that low frequency rTMS, rTMS applied to the dorsolateral prefrontal cortex and cranial electrotherapy stimulation (CES) are effective for reducing pain intensity in chronic pain.

The broad conclusions of this review have not changed substantially for this update. There remains a need for substantially larger, rigorously designed studies, particularly of

longer courses of stimulation. Future evidence may substantially impact upon the presented results. (First published in 2010 and was updated in 2014 and 2018.)

(2017) Goudra B., et al., reported nine trials with 183 patients in each of the groups were included in the analysis. The decrease in pain scores with rTMS was 1.12 (95% confidence interval [CI] being 1.46–0.78) (fixed effects, I2 = 0%, P < 0.001) and in sham-rTMS was 0.28 (95% CI being 0.49–0.07) (Fixed effects, I2 = 0, P = 0.01). The pooled mean drop in pain scores with rTMS therapy was higher by 0.79 (95% CI being 0.26–1.33) (fixed effects, I2 = 0, P < 0.01). The duration and frequency of rTMS were highly variable across trials. Publication bias was unlikely (Egger's test, X-intercept = 0.13, P = 0.75).

The use of rTMS improves the efficacy of conventional medical treatment in chronic pain patients. This treatment is not associated with any direct adverse effects. However, the duration and frequency of rTMS therapy is presently highly variable and needs standardization.

**Obsessive-Compulsive Disease (OCD)**
(2021) UpToDate Reported small, randomized trials suggest that deep brain stimulation (DBS) may reduce symptoms of obsessive-compulsive disorder (OCD), but larger trials are needed to confirm these preliminary findings. DBS is an investigational treatment for incapacitating, treatment-refractory OCD given the invasive nature of DBS and the relative lack of efficacy data.

(2021) Acevedo et al. completed a systematic review on therapeutic neurostimulation in obsessive-compulsive and related disorders which noted invasive and noninvasive neurostimulation therapies for obsessive-compulsive and related disorders (OCRD) were systematically reviewed with the aim of assessing clinical characteristics, methodologies, neuroanatomical substrates, and varied stimulation parameters. Previous reviews have focused on a narrow scope, statistical rather than clinical significance, grouped together heterogenous protocols, and proposed inconclusive outcomes and directions. Herein, a comprehensive and transdiagnostic evaluation of all clinically relevant determinants is presented with translational clinical recommendations and novel response rates. Electroconvulsive therapy (ECT) studies were limited in number and quality but demonstrated greater efficacy than previously identified. Targeting the pre-SMA/SMA is recommended for transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS). TMS yielded superior outcomes, although polarity findings were conflicting, and refinement of frontal/cognitive control protocols may optimize outcomes. For both techniques, standardization of polarity, more treatment sessions (>20), and targeting multiple structures are encouraged. A deep brain stimulation (DBS) 'sweet spot' of the striatum for OCD was proposed, and CBT is strongly encouraged. Tourette's patients showed less variance and reliance on treatment optimization. Several DBS targets achieved consistent, rapid, and sustained clinical response. Analysis of fiber connectivity, as opposed to precise neural regions, should be implemented for target selection. Standardization of protocols is necessary to achieve translational outcomes.

(2021) Liang et al. completed a systematic review and network meta-analysis on the efficacy and tolerability of repetitive transcranial magnetic stimulation for the treatment of obsessive-compulsive disorder in adults. Repetitive transcranial magnetic stimulation (rTMS) has been widely used as an alternative treatment for obsessive-compulsive disorder (OCD). However, the most effective rTMS parameters, such as the targets and stimulation frequencies, remain controversial. Therefore, we aimed to compare and rank the efficacy and tolerability of different rTMS strategies for OCD treatment. We searched five electronic databases from the date of their inception to March 25, 2020. Pairwise meta-analyses and network meta-analyses were performed to synthesize data. We assessed the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. Twenty-two eligible randomized controlled trials (RCTs) were included. For efficacy, low-frequency (LF) rTMS over the dorsolateral prefrontal cortex (DLPFC; mean difference (MD) 6.34, 95% credible interval (CrI) 2.12–10.42) and supplementary motor area (MD 4.18, 95% CrI 0.83–7.62), and high-frequency rTMS over the DLPFC (MD 3.75, 95% CrI 1.04–6.81) were more effective than sham rTMS. Regarding tolerability, all rTMS treatment strategies were similar to the sham rTMS. The estimated ranking probabilities of treatments showed that LF-rTMS over the DLPFC might be the most effective intervention among all rTMS strategies. However, the quality of evidence regarding efficacy was evaluated as very low. Current evidence suggested a marginal advantage for LF-rTMS over the DLPFC on OCD treatment. High-quality RCTs with low selection and performance bias are needed to further verify the efficacy of specific rTMS strategies for the OCD treatment.

(2019) Carmi et al. completed a prospective multicenter randomized double-blind placebo-controlled trial on the efficacy and safety of deep transcranial magnetic stimulation for obsessive-compulsive disorder. They included 11 centers, 99 OCD patients were randomly allocated to treatment with either high-frequency (20 Hz) or sham dTMS and received daily treatments following individualized symptom provocation, for 6 weeks. Clinical response to treatment was determined using the Yale-Brown Obsessive Compulsive Scale (YBOCS), and the primary efficacy endpoint was the change in score from baseline to posttreatment assessment. Additional measures were response rates (defined as a reduction of ≥30% in YBOCS score) at the posttreatment assessment and after another month of follow-up. Eighty-nine percent of the active treatment group and 96% of the sham treatment group completed the study. The reduction in YBOCS score among patients who received active dTMS treatment was significantly greater than among patients who received sham treatment (reductions of 6.0 points and 3.3 points, respectively), with response rates of 38.1% and 11.1%, respectively. At the 1-month follow-up, the response rates were 45.2% in the active treatment group and 17.8% in the sham treatment group. Significant differences between the groups were maintained at follow-up. The authors concluded high frequency dTMS over the medial prefrontal cortex and anterior cingulate cortex significantly improved OCD symptoms and may be considered as a potential intervention for patients who do not respond adequately to pharmacological and psychological interventions but also noted the study had limitations.

The authors identified the following limitations. First, the effect of provocation was not controlled, and the relevant brain activity was not recorded; hence, the exact contribution of the exposure procedure is not fully known. Second, the extent to which the ACC and the mPFC were stimulated needs to be further investigated in functional brain imaging studies. And third, although the patients were asked about their past treatment history, this was not validated with source documentation such as records of filled prescriptions or other objective information. The intriguing finding of an additional benefit for OCD patients who did not respond adequately to pharmacological or psychological treatment suggests that dTMS may involve a different mechanism. Accordingly, we recommend considering the option of adding dTMS to treatment when the response to a proper psychological or pharmacological intervention is inadequate. (This recommendation takes into consideration that the benefit to risk ratio of this treatment is favorable.) It would be optimal if clinicians could predict which patients are likely to respond to treatment. For example, in the pilot study (19) the amplitude of the theta frequency band (4–8 Hz) in response to a Stroop task correlated with the amplitude of the change in YBOCS score. The possibility of corroborating such measures at baseline, after a validation study in a large sample of patients, could help predict the response and selection of the appropriate population for this 6-week treatment course. Further refinements of the stimulation and provocation parameters, treatment during a maintenance phase, and the combination of dTMS treatment with CBT should be investigated. Studies that combine a precise behavioral challenge with neuromodulation and neuroimaging and that attempt to identify potential responders should also be considered. (*ClinicalTrials.gov NCT02229903*)

(2019) Rapinesi et al. completed a systematic review for brain stimulation in obsessive-compulsive disorder (OCD). They reported different add-on stimulation techniques could be effective for severely ill OCD patients unresponsive to drugs and/or behavioural therapy. Most evidence regarded deep brain stimulation (DBS) and transcranial magnetic stimulation (TMS), while there is less evidence regarding transcranial direct current stimulation (tDCS), electroconvulsive therapy, and vagus nerve stimulation (for these last two there are no sham-controlled studies). Low-frequency TMS may be more effective over the supplementary motor area or the orbitofrontal cortex. DBS showed best results when targeting the crossroad between the nucleus accumbens and the ventral capsule or the subthalamic nucleus. Cathodal tDCS may be better than anodal in treating OCD. Limitations. We had to include methodologically inconsistent underpowered studies. The authors concluded different brain stimulation techniques are promising as an add-on treatment of refractory OCD, although studies frequently reported inconsistent results. TMS, DBS, and tDCS could possibly find some use with adequate testing, but their standard methodology still needs to be established.

(2018) Rehn et al completed a meta-analysis of the effectiveness of different cortical targets used in repetitive transcranial magnetic stimulation (rTMS) for the treatment of obsessive-compulsive disorder (OCD). The author’s reported randomized and sham-controlled trials (RCTs) of repetitive transcranial magnetic stimulation (rTMS) in the treatment of obsessive-compulsive disorder (OCD) have yielded conflicting results,

which may be due to the variability in rTMS parameters used. To determine whether rTMS parameters may have influenced treatment effectiveness, studies were further analysed according to cortical target, stimulation frequency, and length of follow-up. Data were obtained from 18 RCTs on rTMS in the treatment of OCD. Overall, rTMS yielded a modest effect in reducing Y-BOCS scores with Hedge's g of 0.79 (95% CI = 0.43-1.15, $p < 0.001$). Stimulation of the supplementary motor area yielded the greatest reductions in Y-BOCS scores relative to other cortical targets. Subgroup analyses suggested that low frequency rTMS was more effective than high frequency rTMS. The effectiveness of rTMS was also greater at 12 weeks follow-up than at four weeks follow-up. The meta-analysis implies that low frequency rTMS applied over the supplementary motor area may offer the greatest effectiveness in the treatment of OCD. The therapeutic effects of rTMS also appear to persist post-treatment and may offer beneficial long-term effectiveness. With the findings, it is suggested that future large-scale studies focus on the supplementary motor area and include follow-up periods of 12 weeks or more.

(2017) Zhou et al. completed an updated meta-analysis on the short-term therapeutic effects of repeated transcranial magnetic stimulation in treating obsessive-compulsive disorder and to examine potential influencing factors. Twenty studies with 791 patients were included. A large effect size (g=0.71; 95%CI, 0.55-0.87; P<0.001) was found for the therapeutic effect. Targeting the supplementary motor area (SMA) (g=0.56; 95%CI, 0.12-1.01; P<0.001), left dorsolateral prefrontal cortex (DLPFC) (g=0.47; 95%CI, 0.02-0.93; P=0.02), bilateral DLPFC (g=0.65; 95%CI, 0.38-0.92; P<0.001) and right DLPFC (g=0.93; 95%CI, 0.70-1.15; P<0.001), excluding the orbitofrontal cortex (OFC) (g=0.56; 95%CI, -0.05-1.18; P=0.07), showed significant improvements over sham treatments. Both low-frequency (g=0.73; 95%CI, 0.50-0.96; P<0.001) and high-frequency (g=0.70; 95%CI, 0.51-0.89; P<0.001) treatments were significantly better than sham treatments, with no significant differences between the effects of the two frequencies. The subgroup analyses indicated that patients who were non-treatment resistant, lacked concurrent major depressive disorder (MDD) and received threshold-intensity rTMS showed larger therapeutic effects than the corresponding subgroups. The subgroup analysis according to sham strategy showed that tilted coils yielded larger effects than sham coils. Meta-regression analyses revealed that none of the continuous variables were significantly associated with the therapeutic effects. The authors concluded based on this study, the short-term therapeutic effects of rTMS are superior to those of sham treatments. The site of stimulation, stimulation frequency and intensity and sham condition were identified as potential factors modulating short-term therapeutic effects. The findings of this study may inspire future research. The authors reported a limitation of only short-term therapeutic effects were assessed in this study.

(2016) Trevizol et al. completed an updated systematic review and meta-analysis on transcranial magnetic stimulation for obsessive compulsive disorder. They included 15 RCTs (n = 483), most had small-to-modest sample sizes. Comparing active versus sham TMS, active stimulation was significantly superior for OCD symptoms (Hedges g = 0.45; 95% confidence interval, 0.2-0.71). The funnel plot showed that the risk of publication bias was low and between-study heterogeneity was low ($I = 43\%$, $P = 0.039$ for the $\chi$

test). Metaregression showed no particular influence of any variable on the results. The authors concluded transcranial magnetic stimulation active was superior to sham stimulation for the amelioration of OCD symptoms. Trials had moderate heterogeneity results, despite different protocols of stimulation used. Further RCTs with larger sample sizes are fundamentally needed to clarify the precise impact of TMS in OCD symptoms.

(2015) Storch et al. completed a review on nine hundred fifty-four adult patients with obsessive-compulsive disorder (OCD), recruited through the Brazilian Research Consortium on Obsessive-Compulsive Spectrum Disorders, were evaluated by experienced clinicians using a structured clinical interview, the Y-BOCS, and the Clinical Global Impressions-Severity scale (CGI-Severity). Similar to results in treatment-seeking children with OCD, our findings demonstrated convergence between the Y-BOCS and global OCD severity assessed by the CGI-Severity (Nagelkerke R(2)=.48). Y-BOCS scores of 0-13 corresponded with 'mild symptoms' (CGI-Severity=0-2), 14-25 with 'moderate symptoms' (CGI-Severity=3), 26-34 with 'moderate-severe symptoms' (CGI-Severity=4) and 35-40 with 'severe symptoms' (CGI-Severity=5-6). Neither age nor ethnicity was associated with Y-BOCS scores, but females demonstrated more severe obsessive-compulsive symptoms than males (d=.34). Time spent on obsessions/compulsions, interference, distress, resistance, and control were significantly related to global OCD severity although the symptom resistance item pairing demonstrated a less robust relationship relative to other components of the Y-BOCS.

The authors noted the following limitations. First, while we had a large, well-characterized clinical sample, there were fewer patients at the extremes of clinical severity. This led to the need to use inference when associating CGI-Severity and Y-BOCS responses across the entire range of scores. However, the use of model-based inference permits the extrapolation of findings to other clinical samples beyond the literal data points employed, provided that the other samples come from the same population (i.e., outpatients with OCD). While the lowest score range of the CGI-Severity addresses the possibility of no functional impairment, we relied on modeling to infer the relationship between the CGI-Severity and Y-BOCS for very low scores (e.g., Y-BOCS scores below 8); in this instance additional sources of clinical information should be incorporated to determine if symptoms have clinical significance (i.e., are impairing). Second, although the sample was comprised of participants from throughout Brazil, findings may not generalize to other geographic regions and to community-based (or non-treatment seeking) samples. Third, the same clinician rated both the Y-BOCS and CGI-Severity; scores on one may have influenced the other. On balance, this method allowed clinicians to have a structured method of ascertaining clinical information, and using two different raters would introduce potential challenges in terms of understanding clinical severity. Finally, no inter-rater reliability checks were employed although raters were experienced clinicians under the supervision of experts in OCD care and research. Within these limitations, this study has significant implications. First, this report objectively defines symptom severity levels that can inform treatment decisions. For example, a patient who presents with a Y-BOCS score of 20 would be classified as having moderate symptoms, indicating that s/he should initiate CBT as the initial intervention. Conversely,

a patient with a Y-BOCS score of 35 would be classified as having symptoms in the severe range, indicating the role of multimodal treatment and/or more intensive CBT. Prior to this study, these evaluations would be subject to clinical judgment without empirical support. Second, these data provide researchers with empirically defined benchmarks to inform inclusion or exclusion criteria that can be individualized for the nature of the study. For example, a study of deep brain stimulation may require that participants have at least moderately severe symptoms for inclusion so as not to expose participants unnecessarily to risk and more costly treatments. Likewise, in clinical trials, response to treatment or resistance/refractoriness can also be more clearly defined in terms of categorical levels of clinical severity. With this in mind, the current study provides guidance as to how this severity threshold would be defined using the Y-BOCS. Finally, these data provide information supporting that those with subthreshold symptoms may experience significant impairment. That Y-BOCS scores in the 14–18 range were best characterized by "Moderate symptoms, functions with effort" underscores the need for further study of this cohort, usually excluded from treatment trials. These data provide empirically based benchmarks on the Y-BOCS for defining the clinical severity of treatment seeking adults with OCD, which can be used for normative comparisons in the clinic and for future research.

**Section Summary: Obsessive Compulsive Disorder**

For individuals who have obsessive-compulsive disorder (OCD) who receive TMS, the evidence includes a number of small-to-moderate sized, sham-controlled, double-blind RCTs and meta-analyses of these studies. Relevant outcomes are symptoms, functional outcomes, and quality of life. A meta-analysis of 15 RCTs (N=483 patients, range 18-65 patients) conducted in 2016 found a benefit of TMS on patient-reported OCD symptom severity at time points ranging from 2 to 6 weeks, but there was substantial variability in the stimulation parameters, including the cortical region that was stimulated and the frequency of stimulation. A meta-analysis conducted in 2021 included 22 RCTs. Three of 5 TMS protocols assessed were significantly more efficacious than sham TMS, and all treatment strategies were similar to sham TMS regarding tolerability. Deep TMS was not more effective than sham TMS, but there was direct evidence from only 1 RCT for this comparison. The overall quality of the evidence was rated very low for efficacy and low for tolerability, and the reviewers concluded that high quality RCTs with low selection and performance bias are needed to further verify the efficacy of specific TMS strategies for OCD treatment. The RCT that was the basis of FDA clearance of deep TMS for treatment of OCD compared deep TMS to sham in 99 patients for 6 weeks, with an additional 4 weeks of follow-up as a secondary outcome. Using a modified intention-to-treat (ITT) analysis (n=94), there was a larger mean decrease from baseline (improvement) on the Yale-Brown Obsessive Compulsive Scale (YBOCS) score (the primary efficacy outcome) in the active treatment group (-6.0 points) than the sham group (-2.8 points), translating to a moderate effect size of 0.69. At 6 weeks, the response rate was 38.1% in the active treatment group compared to 11.1% in the sham group (p=.003), as measured by a 30% or greater increase in the YBOCS. The difference in the primary outcome measure between active and sham groups was not statistically significant in the ITT analysis. There was a benefit for TMS on clinician-reported measures of

improvement, but no significant difference between groups on patient-reported disability and impairment. Additional trials with sufficient sample size and follow-up duration are needed to confirm these results. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

**Posttraumatic Stress Disorder (PTSD)**
(2020) Kan et al. found high - as well as low-frequency rTMS of the right dorsolateral prefrontal cortex (DLPFC) appears to significantly reduce core PTSD symptoms in patients with PTSD. rTMS may therefore be a promising alternative or add-on treatment for PTSD patients who show limited response to antidepressant medication and/or trauma-focused psychotherapy. More high-quality studies are necessary to explore the effects of non-invasive brain stimulation (NIBS) including repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) on different symptom clusters in PTSD.

(2014) Berlim et al. noted the exploratory meta-analysis shows that active rTMS applied to the dorsolateral prefrontal cortex (DLPFC) seems to be effective and acceptable for treating PTSD. However, the small number of subjects included in the analyses limits the generalizability of these findings. Future studies should include larger samples and deliver optimized stimulation parameters.

**Schizophrenia (SZs)**
(2022) Tseng et al. completed a systematic review and network meta-analysis assessment of noninvasive brain stimulation interventions for negative symptoms of schizophrenia which concluded excitatory NIBS protocols over the left dorsolateral prefrontal cortex were associated with significantly large improvements in the severity of negative symptoms. Because relatively few studies were available for inclusion, additional well-designed, large-scale RCTs are warranted.

(2021) Gan et al. completed a double-blind, randomized controlled trial on high frequency repetitive transcranial magnetic stimulation of dorsomedial prefrontal cortex for negative symptoms in patients with schizophrenia. The authors noted negative symptoms are the major challenge in clinical management of schizophrenia. Dorsomedial prefrontal cortex (DMPFC) has been suggested to be highly involved in the mechanisms of negative symptoms of schizophrenia. However, the effect of repetitive Transcranial Magnetic Stimulation (rTMS) over DMPFC has not yet been well studied. In this double-blind, randomized controlled rTMS clinical trial, thirty-three participants (17 in active group and 16 in sham group) were enrolled. This study includes the rTMS treatment phase (lasts for 4 weeks) and a subsequently naturalistic follow-up phase (lasts for another 4 weeks). Schizophrenia patients with prominently negative symptoms were randomly assigned to receive 10 Hz or sham rTMS intervention. The score change in Scale of Negative Symptoms (SANS) was defined as the primary outcome measure. There was a significant decrease in negative symptoms, especially affective flattening and anhedonia in schizophrenia patients after DMPFC-rTMS intervention. Moreover, the negative symptoms improvement could maintain at least another 4 weeks. In addition, no

memory impairment or serious adverse reaction of rTMS emerged. Our results suggest that high frequency rTMS over DMPF may represent a safe and effective treatment for negative symptoms in patients with schizophrenia.

(2021) Guttesen et al. completed a systematic review and meta-analysis for rTMS and transcranial direct current stimulation for auditory hallucinatons in schizophrenia. The authors noted Through imaging studies, a significant increase in cerebral activity has been detected in fronto-temporal areas in patients experiencing auditory verbal hallucinations. Therefore, non-invasive neuromodulation, in particular transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS), has been considered as a therapeutic intervention for medication-resistant auditory verbal hallucinations in schizophrenia. They aimed to synthesize results from randomized trials on either rTMS or tDCS versus placebo in patients with schizophrenia by including five recently published trials in the field. A systematic review and meta-analysis of relevant literature was conducted. Studies were included on the basis of pre-defined selection criteria. The quality of the studies was assessed by the Cochrane Risk of Bias Tool for Randomized Controlled Trials. RevMan 5.3 was used to conduct the statistical analysis. Including 465 and 960 patients, respectively, 12 tDCS and 27 rTMS studies were included. Regarding treatment of medication refractory auditory verbal hallucinations, no significant effect of tDCS (-0.23 [-0.49, 0.02], p = 0.08) or rTMS (-0.19 [-0.50, 0,11], p = 0.21) was found compared to sham in this meta-analysis. The current study found that it cannot be concluded that rTMS and tDCS are efficacious in treating medication-resistant auditory verbal hallucinations. Larger randomized controlled tDCS trials of a higher quality should be conducted in the future to establish substantial evidence of tDCS. The interventions appear safe and may have beneficial effects on other outcomes.

(2020) Guan et al. completed a double-blind, randomized controlled study in veterans with schizophrenia. The authors noted cognitive impairment is a central aspect of schizophrenia (SCZ) that occurs at the onset of the disease and is related to poor social function and outcome in patients with SCZ. Recent literatures have revealed repetitive transcranial magnetic stimulation (rTMS) to be one of the efficient medical interventions for cognitive impairments. However, no study has been conducted to investigate the treatment effectiveness of 20 Hz rTMS with neuronavigation system administered to the left dorsolateral prefrontal cortex (DLPFC) in patients with schizophrenia. In this randomized, double-blind and sham-controlled study, 56 patients were enrolled in 20 Hz rTMS (n = 28) or sham stimulation (n = 28) over left DLPFC for 8 weeks. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) was performed to measure the cognitive function at baseline and after 8 weeks of rTMS treatment. The positive and negative syndrome scales (PANSS) was performed to assess the clinical symptoms at baseline, after 2-week treatment, 4-week treatment, 6-week treatment, and 8-week treatment. Totally, 15 subjects (seven in active group and eight in sham group) dropped out during the trial and the main findings were from completed 41 patients. At 2 weeks, 4 weeks, and 6 weeks, there were no significant differences in PANSS total score and subscores between the sham and treatment groups. At 8 weeks, the 20 Hz rTMS significantly increased the immediate memory score compared with the

sham. Furthermore, the improvement in the immediate memory score was correlated with the decrease in the excitement factor score of the patients with SCZ. Our results suggest that 20 Hz rTMS appears to be an effective treatment for improving the cognitive performance and reducing the clinical symptoms of patients with SCZ.

The authors noted the following limitations: First, there is a relatively small sample size and may have led to false negative or positive results. Findings should be confirmed in a large sample from different ethnic populations. Second, one important limitation of the study was the limited 8-week treatment period and no follow-up, which may not be long enough to assess changes in multiple domains of cognition. Therefore, a follow-up study to investigate the efficacy of rTMS for clinical symptoms and cognitive impairments of SCZ is needed to explore their relationship. Third, the subjects in the study were chronically hospitalized older patients, with a longer illness duration and more severe psychopathology than first episode and drug-naive patients with SCZ or typical psychotic outpatients. This limits the generalization of our findings in this study. Fourth, before this study, they only asked the patients verbally whether they had major life stressor or clinical significant emotional disturbance; however, we did not assess these questions by using a rating scale. Fifth, considering that bilateral stimuli reported in the literatures were more likely to improve cognitive functions such as working memory in SCZ, only the left DLPFC was stimulated in the present study, which was a limitation. Sixth, drug use may have an impact on the cognitive function of patients. In this study, however, substance exposure was not assessed by urine analysis or other methods, but only by self-reported drug use. In summary, the present study indicates that 20 Hz rTMS treatment is beneficial for clinical symptoms and cognitive dysfunction of SCZ. The potential efficacy of 20 Hz rTMS for cognitive dysfunction is important for clinical utilization, since cognitive impairments have been shown to be one of the major obstacles to social dysfunction rehabilitation in patients with SCZ. Thus, rTMS may be a promising cognitive enhancing tool for patients with SCZ as well as other mental disorders. Also, we have found that 20 Hz rTMS is an effective treatment for excited symptoms of SCZ, especially impulse control. Although findings are encouraging, further investigations are necessary to confirm its efficacy for cognitive deficits in a large sample size of first episode and drug-naïve schizophrenia patients in different ethnic populations with a long follow-up period using a longitudinal design.

(2020) Kumar et al. completed a randomized, double blind, sham-controlled trial of repetitive transcranial magnetic stimulation (rTMS) in the treatment of negative symptoms in schizophrenia which aimed to evaluate the efficacy of high-frequency (20 Hz) unilateral rTMS over the left Dorso-Lateral Pre-frontal Cortex (DLPFC) in the improvement of Negative symptoms in Schizophrenia. 100 patients of schizophrenia with predominantly negative symptoms, were enrolled for this randomized, sham-controlled, double-blind trial.Each participant received 20 sessions of rTMS at 20 Hz frequency and 100% motor threshold, via either the active or the sham coil, over 4 weeks. A total of 2000 pulses were imparted in 10 trains per session. Negative symptoms were assessed with the SANS and PANSS. CDSS was used to rule out depressive symptoms. Assessments were carried out at baseline, post-intervention, and 1-month, 2-months, 3-

months and 4-months follow ups. The improvement in the negative symptoms (Anhedonia, Alogia, Avolition, Attention impairment) in active group was statistically significant at 0.01 and 0.05 (p-value) as compared to sham group. The authors concluded these results suggest that high-frequency rTMS may lead to improvement in negative symptoms of schizophrenia. It may be worth considering its use as an adjunct to pharmacological treatment of negative symptoms. The authors did note a major limitation of the study was that we located the DLPFC by manual measurements over the scalp. Even though the "5 cm rule" has been a standard practice, studies have shown that neuro navigational techniques are more accurate in localizing the stimulation site. Also, the study participants continued their respective usual pharmacological interventions during the study period as prescribed by their clinicians. One may argue that this might lead to some confounding of the outcomes. But, no difference in the medications administered to the participants of active or sham group at the baseline. Moreover, they included only those patients who were receiving stable doses of medicines for at least one month, without any recent dose or medication changes. Hence, the chances of medicines being a confounder are low. Continuation of treatment as usual is in keeping with the ethical guidelines as rTMS is not yet a proven exclusive treatment modality for schizophrenia. They did not take an upper limit cut-off for PANSS positive scale scores. This was done to make the study inclusions more representative of the real-world conditions. Nevertheless, since our sample included only the patients who were already on stable treatment, the incidence of positive symptoms in our study was quite low. The maximum PANSS positive scale score in our study sample was 16.

(2020) Li et al. completed a meta-analysis on the efficacy of repetitive transcranial magnetic stimulation on auditory hallucinations in schizophrenia. The authors noted tjeu conducted a meta-analysis of currently available randomized control studies (RCTs). Electronic databases were searched to identify relevant literatures. Only RCTs that met the inclusion criteria were enrolled for further analysis. Standard mean difference (SMD) and 95% confidence interval (CI) values were used to evaluate the effects of rTMS. The overall robustness of the results was assessed by analyzing the influence of single studies. Publication bias was analyzed using funnel plots. Eleven eligible studies were included in this meta-analysis. Auditory hallucinations improved more in the rTMS group than in the sham group (SMD = -0.27, 95%CI = -0.51 to -0.03). However, this result was not stable after sensitivity analysis. Despite a moderate effect for rTMS on AH, future definitive trials of rTMS with rigorous processes and high-quality reporting are needed.

(2019) Jiang et al. reported a total of 9 studies on cognitive dysfunction of SZs were included and involved 351 patients. A significant efficacy of high frequency rTMS on working memory in SZs was found compared to sham stimulation [p = 0.009, standardized mean difference (SMD) = 0.34]. Specifically, rTMS treatment positioned on the left dorsolateral prefrontal cortex (DLPFC), with a total pluses <30,000 was more significantly more effective in improving the working memory (SMD = 0.33, p = 0.03). No improvement was found in other cognitive domains such as executive function, attention, processing speed, and language function. For the follow-up observations, high frequency rTMS had long-lasting sustained effects on working memory (SMD = 0.45, p

= 0.01) and language function (SMD = 0.77, p = 0.02) in SZs. High frequency rTMS over the left DLPFC with a total pulses <30,000 stimulation could significantly improve working memory in SZs for an extended period of time.

(2019) Zhuo et al. completed a randomized, double-blind, sham-controlled trial on repetitive transcranial magnetic stimulation as an adjunctive treatment for negative symptoms and cognitive impairment in patients with schizophrenia. Effective treatment options for negative symptoms and cognitive impairment in patients with schizophrenia are still to be developed. The present study was to examine potential benefits of repetitive transcranial magnetic stimulation (rTMS) to improve negative symptoms and cognition in this patient population. The study was a 4-week, randomized, double-blind sham-controlled trial. Patients with schizophrenia were treated with adjunctive 20-Hz rTMS for 4 weeks or sham condition to the left dorsolateral prefrontal cortex (DLPFC). Negative symptoms were measured using the Scale for the Assessment of Negative Symptoms (SANS) and the Positive and Negative symptom scale (PANSS) negative subscale at baseline and week 4. Cognitive function was measured using the MATRICS Consensus Cognitive Battery (MCCB) at the same two time points. In addition, possible moderators for rTMS treatment efficacy were explored. Sixty patients (33 in the treatment group, 27 in the sham group) completed the study. There was a significant decrease in negative symptoms after 4-week rTMS treatment as measured by the SANS total score and the PANSS negative symptom subscale score. However, there was no significant improvement in cognition with rTMS treatment. Stepwise multiple linear regression analysis suggested that the baseline severity of positive symptoms may predict poorer improvement in negative symptoms at week 4. The authors concluded twenty-Hz rTMS stimulation over left DLPFC as an adjunctive treatment might be beneficial in improving negative symptoms of schizophrenia. Future studies with a longer treatment duration and a larger sample size are needed. (*Clinical trial ID: NCT01940939*)

(2018) Kennedy et al. completed a systematic review and meta-analysis of randomized controlled trials on the efficacy of non-invasive brain stimulation on the symptom dimensions of schizophrenia. They identified 7 RCTs on tDCS (involving 105 participants) and 30 RCTs on rTMS (involving 768 participants). Compared to sham, tDCS improved all symptom dimensions but the effect reached significance for negative symptoms (Hedge's g = -0.63, p = 0.02). Efficacy for positive but not negative symptoms was linearly associated with cumulative tDCS stimulation. Compared to sham, rTMS improved hallucinations (Hedge's g = -0.51, p < 0.001) and negative symptoms (Hedge's g = -0.49, p = 0.01) but was associated with modest, non-significant worsening of positive symptoms (Hedge's g = 0.28, p = 0.13). Higher pulse frequency (>10 Hz), motor threshold intensity of 110%, left prefrontal cortical treatment site and trial duration over 3 weeks were associated with improvement in negative symptoms and worsening in positive symptoms (all p < 0.03). The authors concluded the symptom dimensions in schizophrenia may respond differently to brain stimulation interventions in a way that may reflect the interaction between disease- and treatment-related mechanisms. The findings underscore the need for further research into patient selection prior to treatment assignment and greater refinement of stimulation protocols.

**Section Summary: Schizophrenia**
For individuals who have schizophrenia who receive TMS, the evidence includes a number of sham-controlled, double-blind RCTs and meta-analyses of these studies. Relevant outcomes are symptoms, functional outcomes, and quality of life. Although some evidence suggests that applying transcranial magnetic stimulation (TMS) to the temporoparietal cortex may help with auditory hallucination and positive symptoms, there is insufficient evidence to support or disprove TMS use in the treatment of schizophrenia. In most instances, TMS was used as adjunctive therapy to conventional pharmacotherapy. In these studies, the number of enrolled individuals was small and placebo effect could be a confounding factor. Larger sample sizes and homogeneous clinical variables have not been established. Additionally, studies did not show long term effects and have also shown high frequency repetitive transcranial magnetic stimulation (rTMS) appears to be effective in auditory hallucinations. rTMS at any frequency may be effective for negative symptoms of schizophrenia. The 2020 and 2021 meta-analyses were unable to support or refute the use of rTMS for the treatment of auditory hallucinations (AH) in schizophrenia. Further randomized controlled studies with adequate power are needed to confirm the efficacy of rTMS for the treatment of AH in schizophrenia. However, rTMS appears to be associated with worsening of overall positive symptoms of schizophrenia. Further testing of this hypothesis is needed to refine the use, and parameters of rTMS in individuals with psychosis. A 2019 meta-analysis that reviewed high frequency rTMS as treatment for cognitive deficit in schizophrenia noted individuals who received high frequency rTMS showed acute improvement in specific areas of cognition, specifically executive function and working memory in the short-term; and in working memory and language function in long-term, as compared to the sham. Due to limitations of this analysis, such as small sample size, heterogeneity, a large number of different assessment scales, and the inclusion of a wide range of cognitive domain, there remains limited evidence of the efficacy of rTMS on cognition. Further research is needed using larger sample sizes and rigorous study designs on the use of TMS for auditory hallucinations or negative symptoms of schizophrenia.

**Summary of Evidence**
The available clinical trials for transcranial magnetic stimulation (TMS) as a treatment for medical conditions including but not limited to, bipolar disorder (BD), chronic pain, post traumatic stress disorder (PTSD), and Schizophrenia (SZs) are small, and report mixed results. Larger and more well-controlled clinical trials that address the durability of the potential benefits are needed to explore the therapeutic potential of transcranial magnetic stimulation (TMS).

**Review of Evidence: Transcranial Magnetic Stimulation (TMS) in the Pediatric Population**

**Depression**
(2019) MacMaster et al. found rTMS was effective in reducing major depressive disorder (MDD) symptom severity ($t = 8.94$, $df = 31$, $p < 0.00001$). We observed 18 (56%)

responders (≥ 50% reduction in Ham-D score) and 14 non-responders to rTMS. Fourteen subjects (44%) achieved remission (Ham-D score ≤ 7 post-rTMS). There were no serious adverse events (i.e., seizures). Mild to moderate, self-limiting headaches (19%) and mild neck pain (16%) were reported. Participants ranked rTMS as highly tolerable. The retention rate was 91% and compliance rate (completing all study events) was 99%.

**Summary of Evidence: Transcranial Magnetic Stimulation (TMS) in the Pediatric Population**
Based on review of the peer reviewed medical literature a single center, open trial shows promise that repetitive transcranial magnetic stimulation (rTMS) may be safe and effective treatment for children and adolescents for treatment of resistant major depressive disorder (MDD), however, larger randomized controlled trials are needed to determine the safety and efficacy of this therapy in this patient population. The evidence is insufficient in determining the effects of the technology on net health outcomes.

**Review of Evidence: Additional Transcranial Magnetic Stimulation (TMS) Therapy**
(2022) Hayes Inc. completed an evidence analysis research brief for the reintroduction of rTMS for patients with relapsed or recurrent depression and in summary noted, "there is not currently enough published, peer-reviewed literature to evaluate the evidence related to the reintroduction of rTMS for patients with relapsed or recurrent depression following acute rTMS."

(2014) Dunner et al. completed an observational multisite study on transcranial magnetic stimulation for patients with pharmacoresistant major depressive disorder: durability of benefit over a 1-year follow-up period which stated, adult patients with a primary diagnosis of unipolar, nonpsychotic major depressive disorder (DSM-IV clinical criteria), who did not benefit from antidepressant medication, received TMS treatment in 42 clinical practices. Two hundred fifty-seven patients completed a course of acute TMS treatment and consented to follow-up over 52 weeks. Assessments were obtained at 3, 6, 9, and 12 months. The study was conducted between March 2010 and August 2012.
It compared with pre-TMS baseline, there was a statistically significant reduction in mean total scores on the Clinical Global Impressions-Severity of Illness scale (primary outcome), 9-Item Patient Health Questionnaire, and Inventory of Depressive Symptoms-Self Report (IDS-SR) at the end of acute treatment (all $P < .0001$), which was sustained throughout follow-up (all $P < .0001$). The proportion of patients who achieved remission at the conclusion of acute treatment remained similar at conclusion of the long-term follow-up. Among 120 patients who met IDS-SR response or remission criteria at the end of acute treatment, 75 (62.5%) continued to meet response criteria throughout long-term follow-up. After the first month, when the majority of acute TMS tapering was completed, 93 patients (36.2%) received reintroduction of TMS. In this group, the mean (SD) number of TMS treatment days was 16.2 (21.1). The authors concluded TMS demonstrates a statistically and clinically meaningful durability of acute benefit over 12 months of follow-up. This was observed under a pragmatic regimen of continuation antidepressant medication and access to TMS retreatment for symptom recurrence. The authors also concluded there are limitations to this study. As it had an observational,

naturalistic design, there was no concurrent control population. Conclusions regarding the influence of concomitant treatments, including the role of TMS reintroduction, cannot be fully explored. It should be noted that not all patients had unrestricted access to retreatment or continuation TMS. During the study, insurance coverage for patient access to TMS was gradually introduced in the United States, and therefore patients faced variable degrees of personal financial obligation to pay for TMS. Finally, analysis using an LOCF analysis method may exaggerate the consistency of the scores; however, the low overall discontinuation rate and the similar results in the completer sample lessen the significance of this concern.

**Section Summary: Additional Transcranial Magnetic Stimulation (TMS) Therapy**
Currently there is medically necessary indications for an initial round of sessions/courses, followed by a repeat round of sessions/courses: after remission has occurred, when initial therapy has been successful the repeated request of treatment brings into question treatment durability, and overall value on net health outcomes. There is little medical evidence that additional repeated sessions are of value.

**Review of Evidence: Maintenance Therapy**
(2020) According to Chang et al. the research on acute TMS treatment for treatment-resistant MDD has influenced the development of maintenance TMS treatment guidelines for depression, especially to help decrease or prevent relapse in treatment-resistant MDD patients who had initially responded to acute TMS treatment. TMS, unlike many therapies in medicine, does not suffer from an efficacy/effectiveness gap between clinical trials and clinical treatments. The lack of necessary TMS maintenance protocols after completing acute TMS treatment with full remission may be one of the reasons for the high relapse rates in MDD patients. Therefore, maintenance TMS therapy in line with scheduled TMS frequency attenuation may effectively reduce or prevent the relapse of MDD in treatment resistant MDD patients who had initially responded to acute TMS treatment.

Guidelines are necessary to define treatment course and maintenance appropriateness. Maintenance regimens have not been established and reported outcomes are conflicting. Information is lacking in overall standard of treatment and the lasting effects of participation in TMS. Repetitive transcranial magnetic stimulation had a small short-term effect for improving depression in comparison with sham, but follow-up studies did not show that the small effect will continue for longer periods. There is a lack of evidence supporting the long-term, maintenance effects of TMS.

Based on several studies of maintenance for an individual to continue treatment with transcranial magnetic stimulation (TMS) of the brain as maintenance therapy, the evidence is insufficient in demonstrating an impact on net health outcomes.

**Review of Evidence: Theta burst /Intermittent Theta-Burst Stimulation (iTBS)/Express TMS**

(2021) ECRI published a summary to Theta Burst Transcranial Magnetic Stimulation for Treating Adults with Major Depressive Disorder which noted:
The available clinical trials for TMS as a treatment for medical conditions including but not limited to, bipolar disorder (BD), chronic pain, post traumatic stress disorder (PTSD), and Schizophrenia (SZs) are small, and report mixed results. Larger and more well-controlled clinical trials that address the durability of the potential benefits are needed to explore the therapeutic potential of TMS.

(2021) Voigt et al. completed a systematic review and meta-analysis on theta burse stimulation for the acure treatment of mahor depressive disorder which noted patients with major depressive disorder (MDD) may be refractory to or have contraindications that preclude treatment with antidepressant pharmacotherapies. Alternative therapies such as repetitive transcranial magnetic stimulation (rTMS) continue to evolve, and include theta burst stimulation (TBS), which has advantages over conventional rTMS. The aim of this study was to identify and meta-analyze efficacy data from all randomized controlled trials (RCTs) investigating TBS as a treatment for MDD. Published reports of RCTs (January 1, 2010 to October 23, 2020) were identified via systematic searches in computerized databases, followed by review of individual reports for inclusion. Inclusion criteria included primary diagnosis of MDD ≥ 1 week duration of therapy with ≥10 sessions, and treatment with any form of TBS. The Cochrane GRADE methodology and PRISMA criteria were used for evaluation of individual trials. Data from ten RCTs were included, representing 667 patients. Of these, 8 RCTs compared TBS to sham treatment and one compared TBS to standard rTMS (i.e., high frequency stimulation over left dorsolateral prefrontal cortex [HFL]). Quality of evidence assessment yielded high confidence in the finding of TBS being superior to sham on response measured by the Hamilton Depression Rating Scale (HRSD) (RR = 2.4; 95% CI: 1.27 to 4.55; P = 0.007; I2 = 40%). Comparison of HRSD response rates for TBS versus rTMS produced no statistically significant difference (RR = 1.02; 95% CI: 0.85 to 1.23; P = 0.80; I2 = 0%). The incidence of adverse events between TBS and rTMS was not statistically different. The findings of a positive effect of TBS vs. sham, and noninferiority of TBS vs. standard HFL rTMS support the continued development of TBS to treat depression.

**Summary of Evidence: Theta burst /Intermittent Theta-Burst Stimulation (iTBS)/Express Transcranial Magnetic Stimulation (TMS)**
Based on review of the peer reviewed medical literature utilizing transcranial magnetic stimulation (TMS) as maintenance therapy, Theta TMS/iTBS for all indications except for major depressive disorder (MDD) (*see policy criteria below),* or for additional courses of treatment more medical evidence is needed to support the durability, potential benefits, and the long-term effects of this therapy for these indications. The evidence is insufficient in determining the effects of the technology on net health outcomes.

**Practice Guidelines and Position Statements**

**American Academy of Child and Adolescent Psychiatry (AACAP)**

- (2017) Prior studies suggest that rTMS will play an important role as a neurophysiological probe and therapeutic intervention in future research. Synergistic research with neuroimaging modalities holds the promise of enhancing the efficacy of therapeutic rTMS and informing developmental neuroscience. Ideal future study designs with rTMS and neuroimaging will concurrently address both of these broad goals.

  (2013) Practice parameters on the assessment and treatment of children and adolescents with tic disorders. The Academy did not recommend rTMS, citing lack of empirical support for the treatment of CTD/TD and are not recommended. (*Accessed August 2022*)

**American Psychiatric Association (APA)**

- **Obsessive-Compulsive Disorder**
  (2007; reaffirmed in 2012) In the treatment of patients with obsessive-compulsive disorder have indicated that "findings of the four published trials of rTMS are inconsistent, perhaps because the studies differed in design, stimulation sites, duration, and stimulation parameters. The available results and the technique's non-invasiveness and good tolerability should encourage future research, but the need for daily treatment may limit the use of TMS in practice. (*Accessed August 2022*)
- **Repetitive Transcranial Magnetic Stimulation (rTMS)**
  (2018) The guidelines state, "Multiple randomized controlled trials and published literature have supported the safety and efficacy of rTMS antidepressant therapy." The recommendations include information on the following variables: clinical environment, operator requirements, documentation, coils, cortical targets, coil positioning methods, determination of motor threshold, number of treatment sessions for acute treatment, and allowable psychotropic medications during TMS treatment.
- **Schizophrenia**
  (2020) The APA's practice guideline for the *Treatment of Patients with Schizophrenia* states:
  - Although studies have also been done with TMS for treatment of hallucinations and for treatment of negative symptoms, at present there is insufficient evidence of benefit to suggest use of TMS in individuals with schizophrenia
  - The *Area for Further Research in Individuals with Schizophrenia* notes the following information:
    - Determine the efficacy and comparative effectiveness of neurostimulation approaches (e.g., ECT, TMS) in conjunction with other treatments for schizophrenia

  (*Accessed August 2022*)

**International College of Obsessive-Compulsive Spectrum Disorders (ICOCS)**
(2020) To summarize, LF-rTMS delivered over the SMA (with figure-8 coil) and HF-deep-rTMS over the dorsomedial prefrontal cortex/anterior cingulate cortex (with H7 coil) appear promising interventions in treatment-resistant OCD. There is a pressing need for large replication studies and evaluation of long-term effects/maintenance protocols.

The evidence for tDCS is highly preliminary and further exploratory studies are encouraged. (*Accessed August 2022*)

**National Institute for Health and Care Excellence (NICE)**

- **Transcranial magnetic stimulation for auditory hallucinations**
  (2020) Evidence on the safety of transcranial magnetic stimulation for auditory hallucinations is adequate and raises no major safety concerns. However, evidence on its efficacy is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research. (*Accessed August 2022*)

- **Transcranial Magnetic Stimulation for Obsessive-Compulsive Disorder**
  (2020) Evidence on the safety of transcranial magnetic stimulation for obsessive-compulsive disorder raises no major safety concerns. However, evidence on its efficacy is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research. The guideline states:
  - The evidence on [rTMS] for depression shows no major safety concerns. The evidence on its efficacy in the short-term is adequate, although the clinical response is variable. [RTMS] for depression may be used with normal arrangements for clinical governance and audit.
  - During the consent process, clinicians should inform patients about the other treatment options available, and make sure that patients understand the possibility the procedure may not give them benefit.
  - NICE encourages publication of further evidence on patient selection, details of the precise type and regime of stimulation used, the use of maintenance treatment and long-term outcomes.

  (*Accessed August 2022*)

- **Transcranial Magnetic Stimulation (TMS) for Treating and Preventing Migraines**
  (2014) Evidence on the efficacy of TMS for the treatment of migraine is limited in quantity and for the prevention of migraine is limited in both quality and quantity. Evidence on its safety in the short and medium term is adequate but there is uncertainty about the safety of long-term or frequent use of TMS. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research. (*Accessed August 2022*).

**Clinical Neurophysiology on Theta-Burst Stimulation (TBS) Protocols**
(2020) Lefaucheur et al. Evidence-based Guidelines on the Therapeutic Use of Repetitive Transcranial Magnetic Stimulation (rTMS): These guidelines indicate that although TBS protocols offer the potential advantage of producing similar effects on cortical excitability and plasticity as conventional rTMS protocols during shorter sessions, no firm recommendations can be provided about TBS protocols. (An Update (2014-2018)). (*Accessed June 2022*)

**Regulatory Status**
Below are some of the devices for transcranial magnetic stimulation (TMS) which have been reviewed by the U.S. Food and Drug Administration (FDA). Currently FDA approval for conditions outside of major depression only include obsessive compulsive disorder (OCD). In the management of OCD studies on efficacy are extremely limited The FDA's approval includes the following:

| Device | Manufact-urer | Indication | FDA Clear-ance No. | FDA Clearance Year |
|---|---|---|---|---|
| Apollo | Mag & More | Major Depressive Disorder | K180313 | 2018 |
| Brainsway Deep TMS System | Brainsway | Major Depressive Disorder | K122288 | 2013 |
| Brainsway Deep TMS System | Brainsway | Obsessive-Compulsive Disorder | K183303 | 2019 |
| Cerena | eNeura | Migraine headache with aura | K130556 | 2013 |
| Horizon | Magstim | Major Depressive Disorder | K171051 | 2017 |
| Horizon TMS Therapy System (*Theta Burst Protocol*) | Magstim | Major Depressive Disorder | K182853 | 2019 |
| Magvita | Tonica Elektronik | Major Depressive Disorder | K150641 | 2015 |

| | | | | |
|---|---|---|---|---|
| Mag Vita TMS Therapy System w/ *Theta Burst Stimulation* | Tonica Elektronik | Major Depressive Disorder | K173620 | 2018 |
| Neurosoft | TeleEMG | Major Depressive Disorder | K160309 | 2016 |
| NeuroStar | Neuronetics | Major Depressive Disorder | K083538 | 2008 |
| Nexstim | Nexstim | Major Depressive Disorder | K171902 | 2017 |
| Springtms Total Migraine System | eNeura | Migraine headache with aura | K140094 | 2014 |
| Rapid Therapy System | Magstim | Major Depressive Disorder (*Theta Burst Stimulation iTBS*) | K143531 | 2015 |

*Please note this list is not intended to be all-inclusive.*

# PRIOR APPROVAL

Prior approval is required.

# POLICY

**See Related Medical Policies**
01.01.23 Electrical Stimulation for the Treatment of Muscle Rehabilitation, Pain and Miscellaneous Conditions

**Transcranial Magnetic Stimulation (TMS) for Conditions Outside of Major Depression**
Transcranial Magnetic Stimulation (TMS) is considered **investigational** for all conditions outside of major depressive disorder (MDD) including, but not limited to:

- Amyotrophic lateral sclerosis or motor neuron disease
- Attention deficit hyperactivity disorder
- Bipolar depression
- Bulimia nervosa
- Chronic pain
- Cognitive function in aging
- Epilepsy
- Obsessive-compulsive disorder
- Panic disorder
- Parkinson disease
- Posttraumatic stress disorder
- Schizophrenia
- Substance use disorder
- Suicidality
- Tinnitus

**Additional Courses of Treatment**
Additional sessions or rounds of transcranial magnetic stimulation (TMS) after the initial and repeat treatment courses/episodes, are considered **investigational** due to due to a lack of evidence demonstrating an impact on net health outcomes.

**Maintenance Therapy**
Currently the use of transcranial magnetic stimulation (TMS) as maintenance therapy is considered **investigational** due to a lack of evidence demonstrating an impact on health outcomes.

**Transcranial Magnetic Stimulation (TMS) in the Pediatric Population**
Transcranial magnetic stimulation (TMS) in individuals under **18 years of age** is considered **investigational** due to a lack of evidence demonstrating an impact on net health outcomes.

**Other Types of Transcranial Magnetic Stimulation (TMS)**
All other forms of repetitive transcranial magnetic stimulation (rTMS) are considered **investigational** because the evidence is insufficient to determine the effects of the technology on net health outcomes including, but not limited to the following:

- Accelerated rTMS
- High dose rTMS
- Theta-Burst Transcranial Magnetic Stimulation (iTBS) except for in the treatment of major depressive disorder (MDD)

- Theta-burst TMS (iTBS) for major depressive disorder (MDD) is reviewed on a case-by-case basis.

# PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 90867 Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; initial, including cortical mapping, motor threshold determination, delivery and management
- 90868 Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; subsequent delivery and management, per session
- 90869 Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; subsequent motor threshold re-determination with delivery and management

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| POLICY HISTORY | | |
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| **Date** | **Reason** | **Action** |
| August 2022 | Annual Review | Policy Revised |
| June 2022 | Interim Review | Policy Revised |
| August 2021 | Annual Review | Policy Revised |
| August 2020 | Annual Review | Policy Revised |
| August 2019 | Annual Review | Policy Revised |
| March 2019 | Interim Review | Policy Revised |
| August 2018 | Annual Review | Policy Revised |
| December 2017 | Interim Review | Policy Revised |
| August 2017 | Annual Review | Policy Revised |
| February 2017 | Interim Review | Policy Revised |
| October 2016 | Annual Review | Policy Revised |
| August 2016 | Annual Review | Policy Revised |
| October 2015 | Annual Review | Policy Revised |

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| November 2014 | Annual Review | Policy Revised |
| July 2014 | Interim Review | Policy Renewed |
| January 2014 | Annual Review | Policy Revised |
| January 2013 | Annual Review | Policy Revised |
| January 2012 | Literature Review | New Policy |

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

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